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EXAMINER	
RAWLINGS, STEPHEN L	

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1643	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/533,384	RIDDER ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 October 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *35-39, 42, 43, and 47-49* is/are pending in the application.

4a) Of the above claim(s) *36,37 and 47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *35,38,39,42,43,48 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The election filed October 29, 2008, is acknowledged and has been entered. Claims 40, 41, and 44-46 have been canceled. Claims 35-39, 42, and 47 have been amended. Claims 48 and 49 have been added.

2. Claims 35-39, 42, 43, and 47-49 are pending in the application. Claims 36, 37, and 47 has been withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected species of invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on April 1, 2008.

3. Claims 35, 38, 39, 42, 43, 48, and 49 are currently under prosecution.

Election/Restrictions

4. The elected species of the invention of Group V is a kit comprising reagents to detect p16INK4a and a cell proliferation polypeptide marker, namely Ki67, and which further comprises a p16INK4a sample for carrying out a positive control reaction.

Accordingly, claim 36, as presently amended, has been withdrawn because it is directed to a species of the invention of Group V that is patentably distinct from that of the elected species of the invention in that it is a kit comprising probes for detection of both p16INK4a and p14ARF.

Claim 37, as presently amended, has been withdrawn because it is directed to a species of the invention of Group V that is patentably distinct from that of the elected species of the invention in that it is a kit comprising two probes for detection of two cell proliferation polypeptide markers in biological samples, Ki67 and a second cell proliferation polypeptide marker selected from the group consisting of MCM2, MC5, Ki-S2 PCNA, rpA, and rfc.

Similarly, claim 47, as presently amended, has been withdrawn because it is directed to a species of the invention of Group V that is patentably distinct from that of

the elected species of the invention in that it is a kit comprising two probes for detection of two cell proliferation polypeptide markers in biological samples, Ki67 and MCM2.

Since each of claims 36, 37, and 47 are directed to a species of the invention of Group V that is patentably distinct from that of the elected species of the invention it is proper to withdrawn those claims from further consideration since Applicant has already received an action on the merits for claims directed to the elected, originally presented species of invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Grounds of Objection and Rejection Withdrawn

5. Unless specifically reiterated below, Applicant's amendment has obviated or rendered moot the grounds of objection and rejection set forth in the previous Office action mailed August 1, 2008.

Grounds of Objection Maintained

Specification

6. The objection to the specification because the use of improperly demarcated trademarks is maintained. Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner that might adversely affect their validity as trademarks. See MPEP § 608.01(v).

Although it appears that Applicant may have made a *bona fide* attempt to resolve this deficiency by appropriately amending the specification, an additional example of an improperly demarcated trademark appearing in the specification is noted, namely Tween™; see, e.g., the substitute paragraph at page 26, beginning in line 20.

Appropriate correction is required. Each letter of a trademark should be capitalized or otherwise the trademark should be demarcated with the appropriate symbol indicating its proprietary nature (e.g., ™, ®), and accompanied by generic terminology. Applicants may identify trademarks using the "Trademark" search engine under "USPTO Search Collections" on the Internet at http://www.uspto.gov/web/menu/search.html.

Claim Objections

7. Claim 38 is objected to as being drawn in the alternative to the subject matter of non-elected species of invention.

Grounds of Rejection Maintained

Claim Rejections - 35 USC § 103

8. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

9. The rejection of claims 35, 38, 39, 42, 43, 48, and 49 under 35 U.S.C. 103(a), as being unpatentable over Martin et al. (*Am. J. Pathol.* 2000 May; **156** (5): 1573-1579), is maintained.

Beginning at page 10 of the amendment filed October 29, 2008, Applicant has traversed the propriety of maintaining this ground of rejection.

Applicant's arguments have been carefully considered but not found persuasive for the following reasons:

Martin et al. describes a study in which antibodies that specifically bind to $p16^{INK4a}$ or Ki67 were used; see entire document (e.g., the abstract). Moreover, Martin et al. describes an experiment in which cells expressing $p16^{INK4a}$ and/or Ki67 were "double labeled" with antibodies that bind to $p16^{INK4a}$ or Ki67, so as to permit simultaneous detection of the antigens; see, e.g., page 1574, column 2.

Martin et al. teaches kits comprising reagents for the detection $p16^{INK4a}$ or Ki67 (see, e.g., page 1574, column 2), but does not expressly teach a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen.

Nonetheless, in light of the disclosure by Martin et al., and in view of teachings, suggestions, or other motivation found in the knowledge generally available to one of ordinary skill in the art at the time the invention was made, it would have been obvious to one of ordinary skill in the art at the time to have manufactured a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen, since, in particular, Martin et al. teaches an dual analysis of the levels of $p16^{INK4a}$ and Ki67in cells using detectably labeled antibodies that specifically bind to $p16^{INK4a}$ or Ki67. Given such disclosure, it follows logically that a kit comprising an antibody that specifically binds to $p16^{INK4a}$ and an antibody that specifically binds to the Ki67/Ki-S5 antigen could be used to detect $p16^{INK4a}$ and the Ki67/Ki-S5 antigen; so therefore, one of ordinary skill in the art at the time the invention was made would have been motivated to do so since such kits had become widely used in such research, having established utility in such expression studies, for example, and providing ease of use and convenience, as well as greater uniformity and control.

In addition, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit a “positive control”, namely a sample of $p16^{INK4a}$ polypeptide, which could be used in assays designed to access the presence of $p16^{INK4a}$ in biological samples. The use of such positive controls was routine and conventional at the time. The inclusion of such a positive control in the kit would greatly ease use of the kit to detect $p16^{INK4a}$ in biological samples because it would not have been necessary to develop a positive control, where one has already been provided.

Furthermore, it would have been obvious to one ordinarily skilled in the art at the time the invention was made to include in the kit labeled antibodies that specifically bind to $p16^{INK4a}$ or the Ki67/Ki-S5 antigen since such antibodies could be used directed without the need of secondary antibodies and indirect labeling methods. The inclusion of such labeled antibodies in the kit would greatly ease use of the kit to detect $p16^{INK4a}$ and Ki67 in biological samples because it would not have been necessary to acquire and use secondary antibodies and indirect labeling reagents. There were at the time many different “labels” that might have been used, including, for example, fluorescent labels having different emission spectra, which would permit simultaneous

measurements to be made where more than one fluorescently labeled antibody is used at the same time to stain cells expressing one or both antigens.

Notably, claim 35 has been amended to recite a limitation that the kit comprises primary and secondary antibodies that are obtained from different animals, and Martin et al. teaches primary antibodies that were obtained from mice and secondary antibodies that were obtained from goats; see, e.g., page 1574, column 2. Martin et al. teaches the primary antibodies are labeled with secondary antibodies that are labeled with different enzymes that produced distinguishable detectable signals that permit double labeling of cells and simultaneous analysis of both $p16^{INK4a}$ and Ki67; see, e.g., page 1574, column 2.

Though Martin et al. does not expressly teach that the primary antibodies used were obtained from different animals, since both antibodies were obtained from mice, it would have been *prima facie* obvious to one ordinarily skilled in the art at the time the invention was made to have manufactured the kit using a first primary antibody obtained from one animal (e.g., a mouse) and a second primary antibody obtained from another animal (e.g., a rat) simply because it was so very routine and conventional at the time to use antibodies obtained from different animals (e.g., mice, rats, rabbits, sheep, and goats) at the time. Indeed, it would have been so obvious to do so that it is submitted that this difference need not be explicitly taught or suggested by the reference itself, as the claimed invention would have been an obvious variant of that which is expressly described by the reference given only the knowledge generally available to one of ordinary skill in the art.

Moreover, it is submitted that careful consideration of the record will show that there most definitely was that requisite "something" in the prior art as a whole to suggest the desirability, and thus the obviousness, of combining the teachings of the cited reference and otherwise only the knowledge generally available to one of ordinary skill in the art to thereby make the claimed invention. See *Continental Can Company USA, Inc. v. Monsanto Co.*, 948 F.2d 1264, 1271, 20 USPQ2d 1746, 1751 (Fed. Cir. 1991).

With regard to claim 49, although Martin et al. does not expressly teach that secondary antibody is a rabbit antibody, it would have been *prima facie* obvious to one

ordinarily skilled in the art at the time the invention was made to have manufactured the kit using a secondary antibody obtained from a rabbit simply because it was so very routine and conventional at the time to use rabbit anti-mouse antibodies at the time to perform such indirect analyses. Moreover, the use of a rabbit antibody, as opposed to a goat antibody, as a secondary antibody is an obvious variation, given only the knowledge generally available to one of ordinary skill in the art, and need not be explicitly taught or suggested by the reference itself. As explained, one of ordinary skill in the art at the time the invention was made would have been motivated to produce the kit because such kits had become widely used in such research, having established utility in such expression studies, for example, and providing ease of use and convenience, as well as greater uniformity and control.

It is submitted that this matter represents a clear, "text-book" case of obviousness under 35 U.S.C. § 103.

The claimed kit comprises known compounds, which can be used together in a known way to achieve predictable results.

It is no surprise that one might use a mouse antibody that binds $p16^{INK4a}$ and then a rat antibody, for example, instead of another mouse antibody that binds the Ki67/Ki-S5; similarly it is of no surprise that one might use an anti-mouse goat antibody as a secondary antibody to detect the mouse antibody that binds $p16^{INK4a}$, but an anti-rat hamster antibody as a secondary antibody to detect a rat antibody that binds Ki67/Ki-S5.

Applicant is therefore reminded that "the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield predictable results," *KSR Int'l Co. v. Teleflex Inc.*, 127 S. Ct. 1727, 1739 [82 USPQ2d 1385, 1389] (2007).

Thus, the case of obviousness meets the appropriate standard for obviousness under 35 U.S.C. § 103, since the whole of the claimed process is taught or suggested by the prior art, where there is some teaching, suggestion, incentive, or inference found in the applied references, or in knowledge generally available to the artisan of ordinary

skill in the art, which would have motivated the artisan to practice the claimed invention with a reasonable expectation of success.

Conclusion

10. No claim is allowed.

11. As previously noted in the Office action mailed August 1, 2008, the prior art made of record and not relied upon is considered pertinent to Applicant's disclosure. Both Dai et al. (*Gastroenterol.* 2000 Oct; **119** (4): 929-942) and Emig et al. (*Br. J. Cancer.* 1998 Dec; **78** (12): 1661-1668) teaches an analysis of the levels of p16 and Ki67 in the same samples.

12. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms, Ph.D. can be reached on (571) 272-0832. The fax phone

number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Stephen L. Rawlings/
Primary Examiner, Art Unit 1643

slr
January 28, 2009